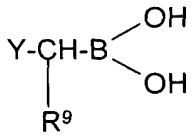
CLAIMS

1. A salt of a pharmaceutically acceptable multivalent metal and an organoboronic acid inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety.

2. A salt of claim 1 wherein the organoboronic acid is of Formula (III):



(III)

wherein

Y comprises a moiety which, together with the fragment $-CH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6, or is $-(CH_2)_m-W$ where m is from 2 to 5 and W is –OH or halogen.

3. A salt of claim 2 wherein R^9 is an alkoxyalkyl group.

4. A salt of claim 2 wherein Y comprises an amino acid which binds to the S2 subsite of thrombin and is linked to $-CH(R^9)-B(OH)_2$ by a peptide linkage, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

5. A salt of claim 4 wherein Y comprises an N-terminally protected dipeptide residue which binds to the S3 and S2 binding sites of thrombin and is linked to $-CH(R^9)-B(OH)_2$ by a peptide linkage.

6. The salt of claim 1 wherein the organoboronic acid has a Ki for thrombin of about 100 nM or less.

7. The salt of claim 5 wherein the Y dipeptide is N-terminally protected or N-terminally unprotected, and the peptide linkages in the dipeptide are unsubstituted or independently N-substituted by a C_1-C_{13} hydrocarbyl, wherein the C_1-C_{13} hydrocarbyl contains no heteratoms or at least one in-chain or in-ring nitrogen, oxygen or sulfur atom, and the C_1-C_{13}

hydrocarbyl is unsubstituted or substituted by a substituent selected from halo, hydroxy and trifluoromethyl.

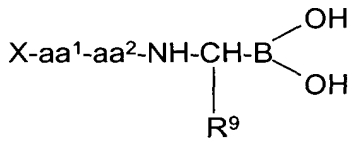
8. The salt of claim 1 wherein the multivalent metal comprises calcium, magnesium or zinc.

9. The salt of claim 1 wherein the salt consists essentially of an acid salt in which one B-OH group of formula (III), when trigonally represented, remains protonated.

10. The salt of claim 7 wherein the salt comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

11. The salt of claim 3 wherein the salt consists essentially of a hemicalcium or hemimagnesium of the organoboronic acid.

12. A salt of a pharmaceutically acceptable multivalent metal and a peptide boronic acid of formula (IV):



(IV)

where:

X is H or an amino-protecting group;

aa^1 is an amino acid residue having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

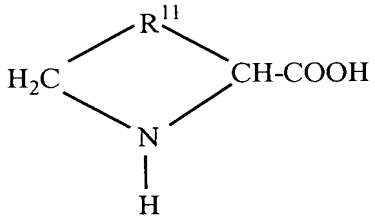
aa^2 is an imino acid residue having from 4 to 6 ring members;

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is -OH, -OMe, -OEt or halogen.

13. The salt of claim 12 wherein aa^1 is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof.

14. The salt of claim 13 wherein aa^1 is of R-configuration.

15. The salt of claim 12 wherein aa^2 is a residue of an imino acid of formula (IV)



(IV),

where R^{11} is $-CH_2-$, $-CH_2-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, and, when the formula (IV) ring is 5- or 6- membered, the formula (IV) ring is unsubstituted or is substituted at one or more $-CH_2-$ groups by from 1 to 3 C_1-C_3 alkyl groups.

16. The salt of claim 15 wherein aa^2 is of S-configuration.

17. The salt of claim 12, wherein aa^1-aa^2 is (R)-Phe-(S)-Pro and the fragment -NH-$CH(R^1)$–$B(OH)_2$ is of R-configuration.

18. The salt of claim 13 wherein the boronic acid is of formula (IX):

X-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$ (IX),

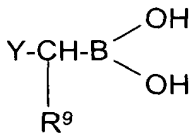
wherein X is R^6-$(CH_2)_p$-C(O)-, R^6-$(CH_2)_p$-$S(O)_2$-, R^6-$(CH_2)_p$-NH-C(O)- or R^6-$(CH_2)_p$-O-C(O)- wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen; amino; nitro; hydroxy; a C_5-C_6 cyclic group; C_1-C_4 alkyl and C_1-C_4 alkyl containing, or linked to the cyclic group through, an in-chain O atom, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a C_5-C_6 cyclic group.

19. The salt of claim 12 which comprises a divalent metal salt of the peptide boronic acid.

20. A pharmaceutical formulation adapted for oral administration which comprises a salt of claim 1.

21. A pharmaceutical formulation adapted for oral administration and comprising

a) a first species selected from a boronic acid of formula (III), and boronate ions of said boronic acid and equilibrium forms of said boronic acid and said boronate ions:



(III)

wherein

Y comprises a moiety which, together with the aminoboronic acid residue -NHCH(R^9)-$B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m$-W where m is from 2, 3, 4 or 5 and W is –OH or halogen; and

(b) a second species selected from multivalent metal ions having a valency n,

wherein the formulation has an observed stoichiometry of first to second species essentially consistent with a notional stoichiometry of n:1.

22. A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising parenterally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt defined in claim 1.

23. A method for preventing thrombosis in a haemodialysis circuit of a patient, for preventing a cardiovascular event in a patient with end stage renal disease, for preventing venous thromboembolic events in a patient receiving chemotherapy through an indwelling catheter, for preventing thromboembolic events in a patient undergoing a lower limb arterial reconstructive procedure, or for treating by way of therapy or prophylaxis an arterial disease selected from acute coronary syndromes, cerebrovascular thrombosis, peripheral arterial occlusion and arterial thrombosis resulting from atrial fibrillation, valvular heart disease, arterio-venous shunts, indwelling catheters or coronary stents, the method comprising

parenterally administering to a mammal a therapeutically effective amount of the salt defined in claim 14.

24. A medicament adapted for oral administration and comprising a therapeutically effective amount of a multivalent metal salt of a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked through a peptide linkage to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1.

25. A medicament of claim 24 which is in solid dosage form.

26. A medicament of claim 25 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

27. A method for making a salt of claim 12, comprising:

combining in a solvent diethanolamine and an ester of a boronic acid as defined in claim 12;

allowing or causing a precipitate to form and recovering the precipitate;

converting the precipitated material into the free organoboronic acid by contacting the precipitated material with an aqueous acid or base; and

reacting the organoboronic acid with a base of a pharmaceutically acceptable multivalent metal to form to a salt as defined in claim 12.